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Docket No.: GPLTD 3.0-002
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kannan et al.

Application No.: 10/762,180 Group Art Unit: 1615

Filed: January 21, 2004 Examiner: Not Yet Assigned

For: CONTROLLED RELEASE MODIFYING COMPLEX AND PHARMACEUTICAL COMPOSITIONS THEREOF

CLAIM FOR PRIORITY AND SUBMISSION OF DOCUMENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant hereby claims priority under 35 U.S.C. 119 based on the following prior foreign application filed in the following foreign country on the date indicated:

Country	Application No.	Date
India	132/MUM/2003	January 31, 2003

In support of this claim, a certified copy of the original foreign application is filed herewith.

Dated: May 25, 2004

Respectfully submitted,

By
John P. Maldjian
Registration No.: 41,967
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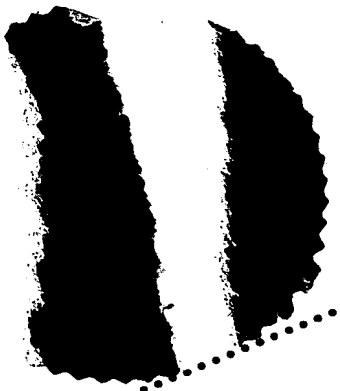
सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional specification filed on 31/01/2003 in respect of Patent Application No.132/MUM/2003 of GLENMARK PHARMACEUTICALS LIMITED, an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026 INDIA

This certificate is issued under the powers vested on me under Section 147 (1) of the Patents Act, 1970.



Dated this 13th day of February 2004.

(R. BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1
THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF A PATENT (Section 5(2),7 and Rule 33A)

We, Glenmark Pharmaceuticals Limited, an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026 INDIA hereby declare

1.(a) that we are in possession of an invention titled **"CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION CONTAINING OR ITS DERIVATIVES AND A PROCESS FOR ITS PREPARATION."**

(b) that the provisional specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are **MUTHAIYYAN ESAKKI KANNAN, ANANDI KRISHNAN** All citizens & residents of India belonging to Glenmark Pharmaceuticals Limited , B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026

3. that we are the assignee of the true and first inventors

4. that our address for service in India is as follows;

Glenmark Pharmaceuticals Limited
Plot No.A-607, T.T.C Industrial Area
M.I.D.C., Mahape
Navi Mumbai – 400 709
INDIA

ORIGINAL

5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed) _____
MUTHAIYYAN ESAKKI KANNAN

(Signed) _____
ANANDI KRISHNAN

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. following are the attachments with the application
(a) Provisional Specification (**18** pages, in triplicate)
(b) Fee Rs. 5000.00 (five thousand rupees only) in bank draft bearing **No. 008805 dated January 28, 2003** drawn on UTI Bank Ltd

We request that a patent may be granted to us for the said invention

Dated this Thirty first (31)st day of January 2003

12/MUM/2003
132/MUM/2003
31/1/2003

GLENN SALDANHA
Managing Director
Glenmark Pharmaceuticals Limited

To,
The Controller of Patents
The Patents Office Branch, Mumbai

भारत सरकार पेटेन्ट कार्यालय शाखा
31 JAN 2003
मुंबई-४०० ०१६.

31/1/03

132 / मुंबई / MUM / 2003 31 JAN 2003

FORM 2

THE PATENTS ACT 1970
(Act 39 of 1970)

PROVISIONAL SPECIFICATION

(SECTION 10)

ORIGINAL

CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION CONTAINING OR ITS DERIVATIVES AND A PROCESS FOR ITS PREPARATION

Glenmark Pharmaceuticals Limited, an Indian Company,
registered under the Indian company's Act 1957 and
having its registered office atB/2, Mahalaxmi Chambers, 22, Bhulabhai
Desai Road, Post Box No. 26511, Mumbai - 400 026, India

THE FOLLOWING SPECIFICATION DESCRIBES THE NATURE OF THE INVENTION.

Introduction

The present invention relates to an extended release pharmaceutical composition, The pharmaceutical composition which contains erythromycin or a derivative thereof is suitable for once-a-day administration and is useful as antibacterial agents. The invention also relates to a process for the preparation of the pharmaceutical composition,

Background of the invention:

Pharmaceutically active medicaments or other active ingredients administrated as conventional tablets or capsules become available to the body fluids at a rate that is initially very high followed by a rapid decline. This delivery pattern of the dosage form results in a transient overdose, followed by a long period of under dosing. This delivery pattern was improved by the development and introduction of controlled/extended release dosage form.

A controlled release dosage form is one that delivers the pharmaceutically active ingredient in a planned, predictable and slower than normal manner for longer period of time at a predetermined rate and thus reducing the drug plasma fluctuation observed when multiple doses of immediate release conventional dosage forms are administered. The most common types of controlled release dosage form are for peroral administration and these dosage forms normally proceed for a 12 or 24 hour dosing interval. Dosing intervals for oral controlled release products beyond once-a-day dosing are limited by physiologic characterization of the gastrointestinal tract.

Erythromycin and its derivatives are well known for their antibacterial activity against a number of organisms and for activities in a number of indications and are typically administered as immediate release compositions, two or three times a day, for a period of about 10 to 14 days.

The recently developed erythromycin derivatives include dirithromycin, roxithromycin, azithromycin, and clarithromycin. All these drugs appear to have essentially similar properties to erythromycin although they may differ in pharmacokinetics.

Clarithromycin, to a lesser extent azithromycin are more active than erythromycin against opportunistic such as mycobacterium avium complex. Clarithromycin is primarily bacteriostatic; it exerts its antimicrobial effect by the inhibition of protein synthesis on bacterial ribosomes. Clarithromycin is active against the major pathogens responsible for respiratory tract infections in immuno-competent patients. Clarithromycin is also active against Helicobacter pylori.

Clarithromycin is rapidly absorbed and its bioavailability after an oral dose of 250 mg. is approximately 55%, which is probably due to the first-pass metabolism, which produces, in particular the 14-hydroxy active metabolite. The maximal serum concentration following oral administration is dose dependent and the time to achieve peak blood concentration is about 2 hours. The food intake slightly delays the onset of absorption and the formation of the active metabolite, but does not affect the extent of the bioavailability. Clarithromycin is lipid soluble and extensively distributed both in body fluids and tissues. Clarithromycin also achieves tissue concentration markedly higher than circulating levels, due to its wide distribution and this aspect is relevant for clinical activity.

The most usual way of peroral administration of clarithromycin is conventional immediate release dosage forms to be taken twice daily, which may lead to a peak and trough blood level fluctuations. The twice daily dosing can result in a poor compliance due to its multiple dosing regimen. The most effective approach to overcome the above mentioned non-compliance causes, has been to develop a controlled release oral solid pharmaceutical composition of clarithromycin.

Certain developmental trials have already been made for solid oral extended release formulations of erythromycin derivatives, preferably clarithromycin.

US Pat. No. 6,010,718 [Filed 11th April, 1997; Assignee: Abbott Laboratories, Issued: 4th Jan, 2000] discloses an extended release formulation of erythromycin derivatives. The formulation comprises an erythromycin derivative and a pharmaceutically acceptable polymer so that, when administered orally, the composition induces significantly lower Cmax in the plasma than an immediate release composition of the erythromycin derivative while maintaining bioavailability and minimum concentration substantially equivalent to that of the immediate release composition of the erythromycin derivative upon multiple dosing.

US Pat. No. 5,705,190 [Filed 19th Dec 1995; Assignee: Abbott Laboratories, Issued: 6th Jan 1998] is directed to a controlled release, oral, solid, pharmaceutical composition for a reduced daily dosage regimen, where the therapeutic ingredient is a poorly soluble basic drug. The formulation comprises the use of a water-soluble alginate salt, a complex salt of alginate acid and an organic carboxylic acid in admixture with the therapeutic drug. A particular embodiment comprising a once a day dosage from for clarithromycin is also described.

US Pat. No. 4,808,411 [Filed June 5; 1987; Assignee: Abbott Laboratories; Issued: February 28; 1989] describes compositions which comprise a complex of carbomer (acrylic acid polymers) and erythromycin or a derivative thereof such as 6-O-methylerythromycin, are disclosed. The compositions provide nontoxic, palatable dry and liquid dosage forms for oral administration.

While all the system mentioned in the above prior art can provide for controlled release of clarithromycin, most of these systems have the disadvantage or drawbacks such as relatively fast drug release profile, lack of stability, variation in drug release profile between the units and difficult expensive manufacturing methods.

It is therefore the main objective of the present invention to design an efficient controlled release pharmaceutical composition that is capable of controlled drug delivery of

erythromycin or its derivative especially . Clarithromycin in order to provide extended therapeutic effects for over 24 hours without dose dumping.

It is another objective of the present invention to develop a controlled delivery system that is relatively easy and inexpensive in preventing dose dumping and providing a better controlled release of erythromycin or its derivative especially. Clarithromycin than the known systems.

Further objective of the present invention is to develop a controlled release pharmaceutical composition containing erythromycin or its derivative especially. Clarithromycin which is, compressible to a size suitable for peroral administration to human beings

Another objective of the present invention is to provide a controlled release pharmaceutical composition containing erythromycin or its derivative especially. Clarithromycin which is also suitable for other high dose erythromycin derivatives.

Yet another objective of the present invention is to provide a controlled release pharmaceutical composition containing erythromycin or its derivative especially. Clarithromycin. which can be introduced into the gastrointestinal tract in solution phase rather than a solid phase thus avoiding any chances of dose dumping.

Still another objective of the present invention is to provide a controlled release pharmaceutical composition containing erythromycin or its derivative especially . Clarithromycin in which the variation in drug release among dosage units is reduced to a minimum.

Another objective of the present invention is to provide a process for the preparation of the controlled release pharmaceutical composition containing erythromycin or its derivative especially .

The above objectives of the present invention are achieved by providing a controlled release pharmaceutical composition comprising of erythromycin or a derivative thereof, a release retarding complex and other required pharmaceutically acceptable additives, in which the release retarding complex comprises of a synergistic effective amount of a primary release retardant, secondary release retardant and an auxiliary release retardant.

Summary of the invention

The present invention is directed to a controlled release pharmaceutical composition of erythromycin or derivatives thereof, said composition comprising a pharmaceutically effective amount of erythromycin or a derivative thereof , a release retarding complex and the other required pharmaceutically acceptable additives. The said release retarding complex essentially comprises, a primary release retardant selected from the low molecular weight polyethylene oxides, a secondary release retardant selected from the high molecular weight polyethylene oxides and an auxiliary release retardant selected from the starch derivatives. The said release retarding complex being present in a synergistic effective amount is sufficient to extend the release of said erythromycin derivatives.

The composition of the present invention in a preferred embodiment , comprises from about 40 percent weight to 60 percent weight of erythromycin or its derivative, preferably clarithromycin, from about 10 percent weight to 50 percent weight of release retarding complex, and other required pharmaceutically acceptable additives.

The pharmaceutical composition of the invention provides erythromycin or its derivative, particularly clarithromycin in a novel release retarding hydrophilic complex matrix which slowly releases the active agent over an extended period of time so as to provide substantial level of plasma concentration of clarithromycin following once-a-day dosing.

In another aspect, the present invention also provides a process for the preparation of the controlled release pharmaceutical composition containing erythromycin or its derivative especially clarithromycin

The said controlled release pharmaceutical composition is prepared according to the present invention by wet granulation, dry granulation, direct compression or by any other technique known in the pharmaceutical art. The composition of the present invention may be optionally coated with a polymer coating, whose materials are not specifically assigned for the modification of the drug release.

Detailed Description of the Invention

The object of the present invention is directed to a controlled release pharmaceutical composition of a pharmaceutically active ingredient, comprise a pharmaceutically active ingredient, a novel release retarding complex and other required pharmaceutically acceptable additives.

As per the present invention the term controlled release means that the therapeutically active ingredient or drug is delivered from the pharmaceutical composition in a planned, predictable and slower than normal manner for a longer period of time at a predetermined rate such that therapeutically beneficial blood levels, devoid of peak and trough fluctuations, of the active ingredient or drug is maintained over an extended period of time. The pharmaceutical composition of the invention is applicable to a wide variety of active pharmaceutical ingredient suitable for use in controlled release formulations.

As a preferred drug, the pharmaceutical composition of the invention includes erythromycin or derivatives thereof, more preferably josamycin, midecamycin, kitamycin, roxithromycin, rokitamycin, oleandomycin, miocamycin, flurithromycin, rosaramicin, azithromycin, and clarithromycin. The above cited pharmaceutically active ingredients are illustrative and non-limiting.

Clarithromycin is a recent erythromycin derivative, having a solubility of about one part in 1000 parts of water. Clarithromycin shows a pH dependent solubility as well as a pH dependent stability profile. At lower pH values, it was found that the clarithromycin exhibited a slight buffer salt effect, which was most pronounced at high pH values. The solubility of clarithromycin was significantly increased at lower pH values. Clarithromycin is well soluble in acidic conditions but unstable in acidic conditions and poorly soluble in alkaline conditions but stable in alkaline conditions.

Clarithromycin is rapidly absorbed and its bioavailability after an oral dose of 250 mg is approximately 55 %, which is probably due to its characteristic pH dependent solubility and stability, and due to its first-pass metabolism, which produces, in particular the 14-hydroxy active metabolite. The maximal serum concentration following oral administration is dose dependent and the time to achieve peak blood concentration is about 2 hours. The food intake slightly delays the onset of absorption and the formation of the active metabolite, but does not affect the extent of the bioavailability. Clarithromycin is lipid soluble and extensively distributed both in body fluids and tissues. Clarithromycin also achieves tissue concentration markedly higher than circulating levels, due to its wide distribution and this aspect is relevant for clinical activity.

The immediate object of the present invention is to develop an efficient controlled release pharmaceutical composition that is capable of controlled drug delivery of erythromycin or its derivative especially clarithromycin, in order to provide extended therapeutic effects for over a period of 24 hours without any dose dumping. The present invention is directed to a controlled release pharmaceutical composition of erythromycin or derivatives thereof, said composition comprising a pharmaceutically effective amount of an erythromycin derivative, a release retarding complex and the other required pharmaceutically acceptable additives. The said release retarding complex essentially comprises, a primary release retardant selected from the low molecular weight polyethylene oxides, a secondary release retardant selected from the high molecular weight polyethylene oxides, and an auxiliary release retardant selected from the starch

derivatives. The said release retarding complex being present in a synergistic effective amount is sufficient to extend the release of said erythromycin derivatives.

As mentioned earlier, the release retarding complex essentially comprises of a low molecular weight polyethylene oxide, a high molecular weight polyethylene oxide and a starch derivative. Polyethylene oxide is a non ionic homopolymer of oxyethylene groups (about 2000 to over 100,000) and they are water soluble. They are thermoplastic materials that are readily calendared, extruded, injection molded or cast. Higher molecular weight polyethylene oxide provides extended release via the hydrophilic matrix approach. Polyethylene oxide on exposure to water or gastric juices, they hydrate and swell rapidly to form hydrogels with properties ideally suited for controlled release formulations. The Polyethylene oxides are non-ionic, so no interaction between the drug and the polymer is to be expected. The primary release retardant of the present invention is selected from the low molecular weight polyethylene oxides, having a molecular weight of atleast 100,000 and the molecular weight range from 100,000 to 900,000. Low molecular weight Polyethylene oxides are commercially available in various grades, under several trade names including Polyox WSR N-10, WSR N-80, WSR N-750, WSR-705, and WSR1105 from The Dow Chemical Co. USA. The different grades under the given trade name represent the differences in oxyethylene contents as well as molecular weight. The pharmaceutical composition of the present invention may contain one low molecular weight polyethylene oxide grade alone or a combination of different grades of low molecular weight polyethylene oxides. All the various grades of polyethylene oxides mentioned above are contemplated to be used in this present invention. For example, the pharmaceutical composition of the present invention contemplates of the use of Polyox WSR N-80 having a molecular weight of 200,000 and showing a viscosity of 55 cPs to 90 cPs for a 5% solution in water at 25°C.

The secondary release retardant of the present invention is selected from the high molecular weight polyethylene oxides having a molecular weight of atleast 1,000,000 and the molecular weight range from 1,000,000 to 7,000,000. High molecular weight Polyethylene oxides are commercially available in various grades, under several trade

names including Polyox WSR N-12K, WSR N-60K, WSR-301, WSR coagulant and WSR-303 from The Dow Chemical Co. USA. The different grades under the given trade name represent the differences in oxyethylene contents as well as molecular weight. The pharmaceutical composition of the present invention may contain one high molecular weight polyethylene oxide grade alone or a combination of different grades of high molecular weight polyethylene oxides. All the various grades of polyethylene oxides mentioned above are contemplated to be used in this present invention. For example, the pharmaceutical composition of the present invention contemplates of the use of Polyox WSR N-60K having a molecular weight of 2,000,000 and showing a viscosity of 2000 cPs to 4000 cPs for a 2% solution in water at 25°C.

The other essential component of the release retarding complex is the auxiliary release retardant, selected from the starch derivatives. Examples of starch derivatives include, Pregelatinized starch, partially pregelatinized starch and retrograded starch. Pregelatinized starch is a starch that has been chemically and /or mechanically processed to rupture all or a part of the starch granules and so renders the starch flowable and directly compressible. Partially pregelatinized starch is a physically modified starch having the benefit of a soluble functionality and an insoluble functionality. Partial pregelatinization breaks the bond between the amylase and amylopectin, which are the two polymers tightly, bound in a specific spherocrystalline structure in starch. The partial pregelatinization process results in partial solubility, increased particle size, improved flow properties and compactability.

Rertrograded starch is a new pregelatinized starch, which is prepared by enzymatic degradation, precipitation (retrogradation) and washing with ethanol. The retrograded pregelatinized starch is a linear oligosaccharide and is characterized by a high specific surface area.

The pharmaceutical composition of the present invention may contain either one of the above starch derivatives alone or a combination of the above starch derivatives as the auxiliary release retardant. All the above starch derivatives are contemplated to be used in

this present invention. For example, the pharmaceutical composition contemplates the use of retrograded pregelatinized starch. The retrograded pregelatinized starch is commercially available as Prejel PA 5 PH from Avebe Inc., The Netherlands.

The low molecular weight polyethylene oxide i.e. the primary release retardant, the high molecular weight release retardant i.e. the secondary release retardant and the retrograded starch i.e. the auxiliary release retardant are present in the pharmaceutical composition of the invention in synergistic effective amounts. When the high molecular weight polyethylene oxide, low molecular weight polyethylene oxide and the retrograded starch are present together as the release retarding complex in the pharmaceutical composition of the invention, the controlled release ability of the composition is more or better than just an additive effect. More specifically, the pharmaceutical composition of the present invention exhibits a better drug release profile when the release retarding complex comprises the above mentioned three components, in the prescribed amounts, than either one by themselves. In another embodiment, the present invention may exhibit a better drug release profile which is devoid of any dose dumping and simultaneously, releasing the complete amount of the drug over a period of 12 hours. As used herein, the term synergistic effective combination of the above mentioned three components in combination to effect a better drug release profile or other improved result in the pharmaceutical composition of the present invention relative to the formulation containing one or the other of the three components or formulations containing any other rate controlling, release retarding polymers.

It is very well within the scope of the present invention, to achieve a controlled release composition, comprises of the pharmaceutically active ingredient, release retarding complex and other required pharmaceutically acceptable additives, where the release retarding complex comprises of the primary release retardant and the auxiliary release retardant only. It is also very well within the scope of the present invention, to achieve a controlled release composition, comprises of the pharmaceutically active ingredient, release retarding complex and other required pharmaceutically acceptable additives.

where the release retarding complex comprises of the secondary release retardant and the auxiliary release retardant only.

The pharmaceutical composition of the present invention is preferably comprised of about 40 percent weight to 60 percent weight of the active pharmaceutical ingredient, erythromycin or derivatives thereof. More preferably, the pharmaceutical composition of the present invention comprised of about 45 percent weight to about 55 percent weight of the erythromycin or derivatives thereof. The pharmaceutical composition of the present invention is comprised of about 10 percent weight to about 50 percent weight of the release retarding complex. More preferably, the pharmaceutical composition of the present invention is comprised of about 30 percent weight to about 45 perdent weight of the release retarding complex. Further more, in a preferred embodiment, the present release retarding complex comprised of the three components in synergistic amounts so as to effect a better drug release.

The pharmaceutical composition of the present invention also contains other required pharmaceutically acceptable additives. The pharmaceutically acceptable additives used in the present invention are selected from the fillers, glidants, and lubricants that are typically used in the pharmaceutical arts for oral solid dosage forms. The filler used herein is inert filler, may be water soluble or water insoluble, and selected from those typically used in the pharmaceutical art for oral solid dosage forms. Examples include calcium carbonate, dicalcium phosphate, tricalcium phosphate, microcrystalline cellulose, monosaccharide, disaccharides, polyhydric alcohols, sucrose, dextrose, lactose, fructose, mannitol, sorbitol, alone or mixtures thereof and the like. The pharmaceutical composition of the present invention contains fillers in amounts ranging from about 1 percent weight to about 90 percent weight. All the various fillers mentioned above are contemplated to be used in the present invention. For example, the pharmaceutical composition of the present invention contemplates the use of lactose as the filler.

The glidants used herein is selected from those glidants typically used in the pharmaceutical art for oral solid dosage forms. Examples include colloidal silicon

dioxide, talc alone or mixtures thereof and the like. The pharmaceutical composition of the present invention contains glidants in amounts ranging from about 0.1 percent weight to about 5.0 percent weight. For example, the pharmaceutical composition of the present invention contemplates the use of talc as the glidant.

The lubricants used herein are selected from those lubricants typically used in the pharmaceutical art for oral solid dosage forms. Examples include stearate salts such as calcium stearate, magnesium stearate, zinc stearate, then others such as stearic acid, talc, hydrogenated vegetable oil, vegetable oil derivatives, silica, silicones, high molecular weight poly alkylene glycol and saturated fatty acids alone or mixtures thereof and the like. The pharmaceutical composition of the present invention contains lubricants in amounts ranging from about 0.1 percent weight to about 5.0 percent weight. For example, the pharmaceutical composition of the present invention contemplates the use of magnesium stearate as the lubricant.

The pharmaceutical composition of the present invention can be optionally coated with a polymer coating, using the polymers / materials not specifically designed for modification of drug release. Examples include cellulose ethers such as hydroxypropyl methyl cellulose, hydroxylpropyl cellulose, others such as polyvinyl pyrrolidone, methacrylic acid derivatives, resins, alone or mixtures thereof and the like. The coating composition comprises of the coating polymer and the other required additives like plasticizer, opacifier, colorant, preservatives and the like. The pharmaceutical composition of the present invention has coating with weight gain ranging from about 0.1 percent weight to about 5.0 percent weight. For example, the pharmaceutical composition of the present invention contemplates the use of hydroxypropyl methyl cellulose along with the other required additives as the coating material.

The pharmaceutical composition of the present invention may contain other optional ingredients that are also typically used in pharmaceuticals such as coloring agents, preservatives, flavorants, and the like. These optional ingredients, if present are

preferably present in amounts ranging from about 0.1 percent weight to about 5.0 percent weight of the dosage form.

The pharmaceutical composition of the present invention can be prepared by wet granulation, dry granulation, and direct compression or by any other technique known in the pharmaceutical art. In one aspect of the invention, the pharmaceutical composition of the present invention can be prepared by wet granulation.

The wet granulation process comprising of the following steps. (1) Dry blending of the mixture of erythromycin derivative, primary release retardant, secondary release retardant, auxiliary release retardant and other required pharmaceutically acceptable additives to make a uniform homogenous blend. (2) Wet granulating the uniform blend. (3) Diminuting the wet mass. (4) Drying and sizing the granules to an optimum size suitable for compression. (5) Blending the sized granules with the required pharmaceutically acceptable additives/lubricants. (6) Compressing the blended granules into tablets.

In another aspect of the invention, the homogenous blend of the active ingredient, the primary release retardant, the secondary release retardant, the auxiliary release retardant and the other required pharmaceutically acceptable additives is compacted into slugs or ribbons using a roller compactor. The slugs or ribbons are reduced to the desired size, then lubricated and compressed into tablets.

In a further aspect of the invention, the homogenous blend of the active ingredient, the primary release retardant, the secondary release retardant, the auxiliary release retardant and the other required pharmaceutically acceptable additives is directly compressed into tablets. The pharmaceutical composition of the present invention can be prepared by any other technique known in the pharmaceutical art.

In all of the above illustrated process for the preparation, preferably the pharmaceutical composition is compressed into a tablet form which is of the order of 150 N to 350 N and

more preferably 200 N to 300 N as determined by a Schleuniger hardness tester. The compressed tablets are optionally coated with a polymer not specifically designed for modification of drug release.

The pharmaceutical composition of the present invention in oral solid dosage form i.e. tablet form shows a better controlled drug release profile, devoid of any dose dumping and simultaneously with insignificant variation between the individual units of the dosage form of the invention.

The controlled release pharmaceutical composition of the invention is provided in oral solid dosage form, conveniently in a unit dosage form, more conveniently in a tablet dosage form. Preferably, the tablet dosage form is intended to release the active ingredient slowly in a controlled, predetermined, predictable rate after oral administration within the body as the dosage form progresses along the gastrointestinal tract. The presence of synergistic effective amounts of the low molecular weight polyethylene oxide, high molecular weight polyethylene oxide in combination with the retrograded starch provides a better controlled drug release profile without dose dumping. When used in the amounts provided, the drug release profile is substantially better than the drug release profile using either low molecular weight polyethylene oxide, or high molecular weight polyethylene oxide or retrograded starch.

The pharmaceutical composition of the present invention shows a predictable and predetermined controlled drug release, so that the active ingredient is available over a period up to 24 hours, depending upon the precise tablet size, the identity of the active ingredient, aqueous solubility of the active ingredient, hardness and particular composition of the release retarding complex. Furthermore, the composition prepared on accordance with the present invention is hard, have low friability and provide controlled and sustained release over an extended period. Finally the drug release profile of each unit dosage form is uniform and without any significant variation. The oral solid dosage form prepared by the present invention are stable and their drug release rate does not change to any significant, if any, extent over an extended period of storage.

Moreover, it has been found that the pharmaceutical composition of the invention having the combination of the low molecular weight polyethylene oxide, high molecular weight polyethylene oxide and the retrograded starch in the synergistic amounts provided herein above give drug release profile that may be obtained using a different controlled release polymer (s), but in those cases, the dose dumping during the initial duration and variation in drug release profile between the unit dosage units is high.

The following non-limiting examples further illustrate the present invention. Unless indicated to the contrary; all percentages are weight percentages relative to the unit dosage form.

Example-1

Table 1.

Sr. No.	*Ingredient*	*Quantity per unit dosage form*
1.	Clarithromycin	500.0
2.	Polyethylene oxide (Mol. Wt.:200,00)	145.0
3.	Polyethylene oxide (Mol. Wt.:2,000,00)	60.0
4.	Retrograded starch	145.0
5.	Lactose Monohydrate	105.0
6.	Talc	30.0
7.	Magnesium Stearate	15.0
8.	Purified Water	q.s

The ingredients 1 to 5 mentioned in Table 1 was sifted through ASTM mesh no. 40, blended together in a blender to a homogenous blend. The homogenous blend was

granulated with water, the granules were dried in a fluid bed drier. The dried granules were reduced or sized to ASTM mesh no. 16 granules and then lubricated with talc and magnesium stearate. The lubricated granules were compressed to tablets

The drug release profile from the oral solid tablet dosage form of the invention was studied in pH 5.0 acetate buffer in USP Dissolution Apparatus Type II, 50 RPM at 37°C and the results are tabulated below.

Table 2

Drug Release Profile

Time (h)	*% Cumulative Drug Released*
1	7.0
2	14.0
4	30.0
6	46.0
8	62.0
10	76.0
12	88.0

The drug releases from the oral solid tablet dosage form according to the Example 1were extended up to 12 h.

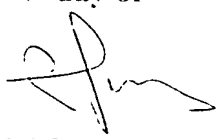
From the Table 2 it should be clear that the pharmaceutical composition defined in the Example 1 of the present invention shows a predictable and predetermined controlled drug release profile devoid of dose dumping and the drug release was complete over duration of 12 hours. The difference between the drug releases from individual unit dosage forms is insignificant.

The drug release profile of the drug defined in Example 1 of the present invention was compared with the reference marketed product, Biaxin XL 500 mg Film Coated Tablets manufactured by Abbott Laboratories, in pH 5.0 acetate buffer using USP Dissolution Apparatus Type II at 50 RPM. The results were found to be comparable and the f2 value was found to be above 50.

Advantages of the present invention

- Provides a controlled release pharmaceutical composition containing erythromycin or its derivative especially clarithromycin in an oral solid dosage form, conveniently in a unit dosage form, more conveniently in a tablet dosage form.
- The controlled release pharmaceutical composition is suitable for other high dose erythromycin derivatives.
- The controlled release composition is useful for administration into the gastrointestinal tract in solution phase rather than a solid phase thus avoiding any chances of dose dumping.
- The controlled release pharmaceutical composition provides a dosage form in which the variation in drug release among dosage units is reduced to a minimum.
- The compositions has an improved taste profile and reduced gastrointestinal side effects as compared to those for the immediate release composition.

Dated this Thirty first (31)st **day of** **January** **2003**



(GLENN SALDANHA)

Managing Director

Glenmark Pharmaceuticals Limited